Exhibit 118

TOXICOLOGICAL PROFILE FOR CHROMIUM

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3.5.2 Mechanisms of Toxicity

The toxic potency of chromium is dependent on the oxidation state of the chromium atom, with chromium(VI) more potent than chromium(III). The mechanisms of chromium toxicity and carcinogenicity are very complex. They are mediated partly through reactive intermediates during intracellular reduction of chromium(VI) to chromium(III) and oxidative reactions, and partly mediated by chromium(III) which is the final product of intracellar chromium(VI) reduction and forms deleterious complexes with critical target macromolecules (Chen and Shi 2002; Costa 2003; Costa and Klein 2006a; Ding and Shi 2002; Jeejeebhoy 1999; Levina and Lay 2005; Liu and Shi 2001; O'Brien et al. 2003; Paustenbach et al. 2003; Salnikow and Zhitkovich 2008; Shrivastava et al. 2002; Yao et al. 2008; Zhitkovich 2005). Chromium(III) may form complexes with peptides, proteins, and DNA, resulting in DNA-protein crosslinks, DNA strand breaks, and alterations in cellular signaling pathways, which may contribute to toxicity and carcinogenicity of chromium compounds.

The greater toxic potency of chromium(VI) relative to chromium(III) most likely is related to two factors: (1) the higher redox potential of chromium(VI) (Levina and Lay 2005; Reddy and Chinthamreddy 1999); and (2) the greater ability of chromium(VI) to enter cells (Costa 2003). Differences in molecular structure contribute the greater cellular uptake of chromium(VI) compared to chromium(III) (Costa 2003; Costa and Klein 2006a). At physiological pH, chromium(VI) exists as the tetrahedral chromate anion, resembling the forms of other natural anions (e.g., sulfate and phosphate) which are permeable across nonselective membrane channels. Chromium(III), however, forms octahedral complexes and cannot easily enter through these channels. Therefore, the lower toxicity to chromium(III) may be due in part to lack of penetration through cell membranes. It follows that extracellular reduction of chromium(VI) to chromium(III) may result in a decreased penetration of chromium into cells, and therefore, a decreased toxicity.

The higher redox potential of chromium(VI) contributes to the higher toxic potency of chromium(VI) relative to chromium(III) (Levina and Lay 2005), because once it is taken into cells, chromium(VI) is rapidly reduced to chromium(III), with chromium(V) and chromium(IV) as intermediates. These reactions commonly involve intracellular species, such as ascorbate, glutathione, or amino acids (Aiyar et al. 1991; Blankenship et al. 1997; Capellmann et al. 1995; Hojo and Satomi 1991; Kim and Yurkow 1996; Lin et al. 1992; Liu et al. 1997b; Mao et al. 1995; Wiegand et al. 1984; Zhitkovich et al. 1996). Chromium(VI), chromium(V), and chromium(IV) have all been shown to be involved in Fenton-like oxidative cycling, generating oxygen radical species (Aiyar et al. 1991; Chen et al. 1997; Liu et al. 1997b;

Luo et al. 1996; Mao et al. 1995; Molyneux and Davies 1995; Tsou et al. 1996). It is believed that the formation of these radicals, which leads to oxidative stress, may be responsible for many of the deleterious effects of chromium on cells, including lipid peroxidation (Bagchi et al. 2002a; Hojo et al. 1999, 2000) and alterations in cellular communication, signaling pathways and cytoskeleton (Chen et al. 1997; Gao et al. 2002; Gunaratnam and Grant 2002, 2004; Kim and Yurkow 1996; Mikalsen 1990; O'Hara et al. 2007; Shumilla et al. 1998; Wang et al. 1996a; Xu et al. 1996; Yao et al. 2008; Ye et al. 1995). The chromium(VI)-induced oxidative stress resulting from the generation of reactive oxygen species has been shown in *in vitro* studies to result in the induction and inhibition of the transcription factors, NF-κB and AP-1, activation of p53, activation of hypoxia-inducible factor 1 (HIF-1), cell-cycle arrest, and p53-dependent apoptosis (Yao et al. 2008). Cellular damage from exposure to various chromium compounds can be blocked by radical scavengers, further strengthening the hypothesis that oxygen radicals play a key role in chromium toxicity (Hojo et al. 2000; Luo et al. 1996; Tsou et al. 1996; Ueno et al. 1995a).

The products of metabolic reduction of chromium(VI) (free radicals and chromium(IV) and (V)) and the newly generated chromium(III) are thought to be in part responsible for the carcinogenic effects seen in human and animal studies. The interaction of free radicals, chromium(V), chromium(IV), and chromium(III) with DNA can result in structural DNA damage, functional damage, and other cellular effects (Levina and Lay 2005; Singh et al. 1998a). The types of chromium-induced structural damage include DNA strand breaks (Aiyar et al. 1991; Bagchi et al. 2002a; Bryant et al. 2006; Casadevall et al. 1999; Ha et al. 2004; Kuykendall et al. 1996; Manning et al. 1992; Messer et al. 2006; Pattison et al. 2001; Ueno et al. 1995a), DNA-protein crosslinks (Aiyar et al. 1991; Blankenship et al. 1997; Capellmann et al. 1995; Costa et al. 1996, 1997; Kuykendall et al. 1996; Lin et al. 1992; Manning et al. 1992; Mattagajasingh and Misra 1996; Miller et al. 1991; O'Brien et al. 2005; Quievryn et al. 2001; Zhitkovich et al. 1996), DNA-DNA interstrand crosslinks (Xu et al. 1996), chromium-DNA adducts, and chromosomal aberrations (Blankenship et al. 1997; Sugiyama et al. 1986a; Umeda and Nishimura 1979; Wise et al. 1993). Functional damage includes DNA polymerase arrest (Bridgewater et al. 1994a, 1994b, 1998), RNA polymerase arrest, mutagenesis, and altered gene expression. However, DNA double strand breaks may not be due to free radical formation, but due to the formation of chromium-DNA ternary adducts, which lead to repair errors and collapsed replication forks (Ha et al. 2004). Double strand breaks can also lead to alterations in cellular communication and effects on signaling pathways and cytoskeleton. In addition, results of recent studies in human lung cells suggest that chromosome instability is an important mechanism in the development of lung cancers; specifically, chromium-induced chromosome

instability appears to be mediated through centrosome and spindle assembly checkpoint bypass (Holmes et al. 2006; Wise et al. 2006a).

Location of particle deposition in the lung and extracellular dissolution of chromium(VI) compounds (e.g., solubility) are also important considerations regarding the mechanism of chromium(VI)-induced carcinogenesis. In chromate workers, analysis of bronchial tissues shows higher chromium concentrations in areas of bronchial bifurcation compared to other areas in the bronchi (Ishikawa et al. 1994a). Also, autopsy results show that some precancerous bronchial lesions originated at bronchial bifurcations (Ishikawa et al. 1994b). Solubility of chromium(VI) compounds may also play a role in carcinogenic potency, with extracellular dissolution of the chromium compound critical to activity (Wise et al. 2004). This hypothesis is supported by *in vitro* data suggesting that extracellular chromium ions are the proximate clastogen in Chinese hamster ovary cells (Wise et al. 2004).

Chromium(III) can also interact with DNA to form adducts/complexes and DNA-protein crosslinks that interfere with DNA replication and transcription, and can promote the expression of regulatory genes such as nuclear factor-κβ, or may inhibit regulatory genes such as GRP78 (Chen et al. 1997; Kim and Yurkow 1996; Manning et al. 1992; Mikalsen 1990; O'Hara et al. 2003; Shumilla et al. 1998; Wang et al. 1996a; Xu et al. 1996; Ye et al. 1995). Disruption of these pathways by other compounds has been implicated in carcinogenesis. The structural and functional damage can lead to growth arrest (Xu et al. 1996) and apoptosis (Carlisle et al. 2000; Singh et al. 1999). Numerous studies show that chromium can induce apoptosis (Asatiani et al. 2004; Bagchi et al. 2001; Carlisle et al. 2000; Flores and Perez 1999; Gambelunghe et al. 2006; Gunaratnam and Grant 2002, 2004; He et al. 2007; Manygoats et al. 2002; Petit et al. 2004; Russo et al. 2005; Vasant et al. 2003); although the mechanism by which chromium induces apoptosis is not fully understood, it is believed to involve oxidative stress and activation of the p-53 protein (Pulido and Parrish 2003; Singh et al. 1998a).

3.5.3 Animal-to-Human Extrapolations

Species-related differences in chromium pharmacokinetics have been demonstrated, both between rodent species and between rodents and humans. However, studies directly examining species differences have been limited. Human microsomal chromium(VI) reduction is different from the P450-mediated microsomal reduction in rodents; specifically, the human system is much less oxygen-sensitive, has a much greater affinity for chromate, and is apparently mediated by flavoproteins (Myers and Myers 1998; Pratt and Myers 1993). Tissue distributions of chromium were found to be different between rats and